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STUDY OF THE TAUTOMERISM OF THE SALTS OF 1-PHENYL-4, 5-DIHYDRO-5-OXY-3-TRIAZOLYL METHYL SULFONE

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A STUDY OF THE TAUTOMERISM OF THE SALTS OF 1-PHENYL-4,5-DIHYDRO-5-OXY-3-TRIAZOLYL METHYL SULFONE

BY

EDWARD HYATT WIGHT

A THESIS SUBMITTED FOR
THE DEGREE OF MASTER OF SCIENCE

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Introduction

The subject of tautomerism has long been one of great discussion and speculation. Some of the most important generalisations I shall here attempt to state as follows:

Comstock's Theory

The potassium and silver salts of tautomeric amides have different but definite structures, the potassium salt being a nitrogen compound, while the silver salt is an oxygen compound.

Wheeler's Theory

When two isomeric products are formed from the salt of a tautomeric acid and a reagent, one of the products is formed from the salt and the other by a rearrangement of the first. In the case of the amides, the oxygen derivatives were supposedly formed first and these reacting with alkylhalide gave the nitrogen esters.

Michael's and Nef's Theory

When the salt of a tautomeric compound reacts with another reagent to give two isomeric products, one is formed by direct substitution of the metal, and the other by the decomposition of an unstable intermediate addition product formed by the union of the salt and the other reagent.

Although these theories apply in certain cases, their applicability is not general enough to accept them as final, as has been shown most clearly by Acree and his coworkers by their work on the Urazoles and their derivatives.[1]

Acree's Theory

Now Acree's theory, in brief, states:

When a tautomeric compound yields two or more derivatives, it does so because there is one tautomeric form which yields two or more derivatives through independent side reactions, or there are two or more forms in equilibrium, each of which gives its own derivatives independently of the other. The latter view seems to be the most acceptable.

Although, as yet, the theory[2] is only tentative, and needs more substantiation before acceptance, there are no facts known which do not fit the theory harmoniously.

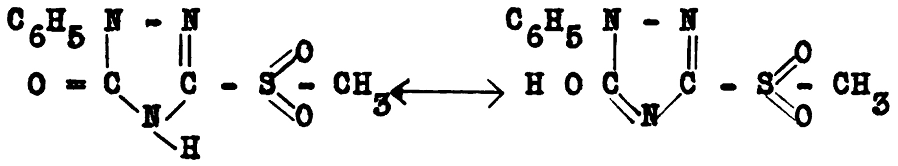
The substance investigated in the present study is 1-phenyl-4,5-dihydro-5-oxy-3-triazolyl methyl sulfone which has been shown by Lubs and Esslinger[3] to have the following structure:

---

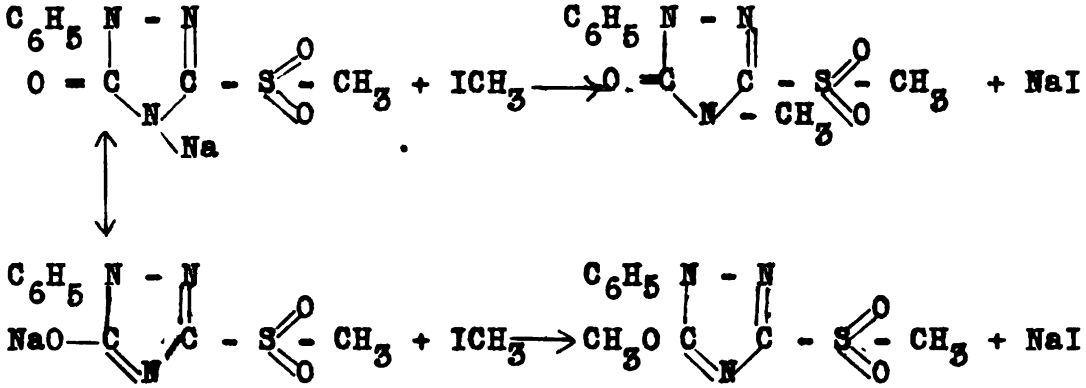
[1] Acree's work on Urazoles, Ber. d. Deut. Chem. Ges. 41, 3207. Lub's Dissertation J. H. U. 1914.

[2] American Chemical Journal 38, 1 & 8.

[3] Esslinger Dissertation J. H. U. 1912.



The free acid and salts may exist in two tautomeric forms as follows:



If such a salt reacts with the alkyl halide through its ions, or molecules, or both, the reaction velocities can be expressed as follows:

$$\text{I.} \quad \frac{dx}{dt} = K \cdot C_{salt} \cdot C_{ester}$$

$$\text{II.} \quad \frac{dx'}{dt} = K' \cdot C_{salt} \cdot C_{ester}$$

where x and x' represent the N-ester and O-ester, respectively.

By addition $\frac{d(x + x')}{dt} = (K + K')\, C_{salt} \cdot C_{ester}$

By division $\frac{x}{x'} = \frac{K}{K'}$

These equations then show that the total esters are formed by a bimolecular reaction, and that the ratio of the N-ester

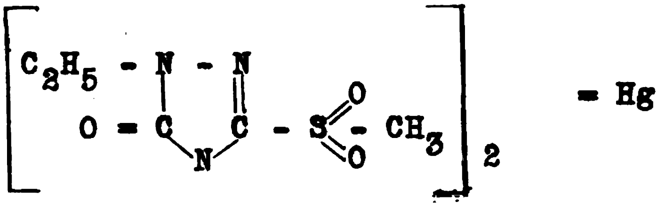
and O-ester should be constant if each ester is formed entirely from the salt directly instead of by a total or partial rearrangement of the other ester. The object of the present work is to study the ratios of esters in order to learn whether these esters are formed by the independent side reactions given above or whether subsequent rearrangements of these are brought about by the alkyl halides.

It may be stated at once, that in a given solvent, the ratio of esters from a given salt and alkyl halide is constant. Not only do we have this proof that each ester is formed entirely and directly from the urazole salt but this is substantiated by the proof that neither the N-ester nor the O-ester rearranges in the presence of the alkyl halide.

This shows conclusively that each ester, once formed, is stable, and that the equations given, harmonize with the facts which have been established experimentally. We may conclude, therefore, that the mercury salt may exist in the two tautomeric forms given above, each of which reacts independently with the alkyl halide and yields the corresponding ester.

Experimental

Mercury Salt of 1-Phenyl-4,5-dihydro-5-oxy-3-triazolyl Methyl Sulfone:



The mercurous salts can not be used to prepare this salt, as they are insoluble or unstable in neutral solutions. If acid solution be used, the sulfone is thrown down by the excess H^+ ion which drives back the dissociation of the urazole and makes it insoluble.

Preparation

A known weight of methyl sulfone was used. This was put into solution by addition of an equivalent quantity of NaOH, which forms the soluble Na salt.

This may also be done by addition of NaOH solution from a burette until solution reacts alkaline. Phenolphthalein is used as an indicator. To the solution of the soluble Na salt is added a neutral solution of $HgCl_2$ until the addition of more $HgCl_2$ forms no precipitate.

The mercury salt of the methyl sulfone precipitates out as a beautiful white powder. This salt may be filtered off and washed with hot water frequently. It

is then dried in air and kept in a dessicator. A quantitative yield is obtained.

Water of Crystallization

Weight of salt 0.5525 gm. heated 110° for 10 hrs.
Weight of salt 0.5045 gm. after heating.

This calculation gives about 3 molecules of water of crystallization.

Methods of Preparation of the Esters from the Mercury Salt and CH_3I and the Method of Extraction:

It was found that the method used by Lubs for the extraction of esters formed by treating the Hg salt with alkyl iodide could not be used in this case:

First.-- Unlike the AgI which is insoluble in the reagents used, the HgI_2 formed is soluble in ether and in chloroform (to 0.04 pt. per 100 pts.), and, hence, could not be absolutely separated from the solution mixture by filtration. Thus, upon evaporation, one would get an excess weight of esters.

Second.--The HgI_2 is insoluble in H_2O, but the esters are also.

Third.--Like a great many other salts, HgI_2 forms, in solution with KCN, a complex salt of the formula probably $(HgCN_4)K_2$, very soluble in H_2O.

Hence, we have a way to eliminate the HgI_2 from the $CHCl_3$ extract and to convert the insoluble HgI_2 into a soluble salt.

A solution of this salt $(HgCN_4)K_2$ was extracted with 40 c.c. $CHCl_3$ in 20 c.c. portions and upon evaporation of the $CHCl_3$ there was a residue of 0.0005 gms. which is equivalent to 0.05 per cent error with the weights used.

Purification of $CHCl_3$

Chloroform was extracted with acid and then boiled with a solution of KOH for two hours, using a reflux condenser. After separation, it stood in contact with $CaCl_2$ (fused) over night. It was filtered the next day and distilled off from solid KOH.

Preparation of KCN Solution

The amount of potassium cyanide used was such that three cubic centimeters of the solution would contain enough of the salt KCN to form the complex salt above with all the Hg set free from 0.5 gm. of methyl sulfone if the methylation had been complete. A KCN solution may be standardized by $HgNO_3$:

$KCN + KI + HgNO_3$, end point cloudy formation HgI. The potassium cyanide solution is filtered through three thicknesses of paper. It is then extracted with $CHCl_3$ portions of 15 c.c. until, upon evaporation of the $CHCl_3$ portion, no weighable residue is left.

Solubility of Esters in KCN Solution

Esters stood in contace with a KCN solution for four hours. The solution taken up with a pipette and extracted with $CHCl_3$ gave no residue upon evaporation. If, by chance, some ester was dissolved in KCN solution, it would be taken up by $CHCl_3$, in which it is so much more soluble.

The ester being insoluble in H_2O, which is used to wash the reaction mixture, would also tend to be taken up by $CHCl_3$, and thus is freed from KCN soluble in H_2O.

Solubility of Solvent ~~Used~~ in Water

Such solvents as alcohol,ether, and benzene, which are soluble, or partially soluble, in the water, might cause a loss in ester; but ether being soluble in all proportions in $CHCl_3$, should be taken up entirely by successive extractions as was found to be the case. Benzene, being soluble in $CHCl_3$, but insoluble in H_2O, or almost insoluble in water, will cause no loss in ester.

Alcohol is soluble in all proportions in water and also in $CHCl_3$. Hence, in this case, there arise difficulties,as is shown from the small yields of esters obtained by one extraction. However, it was found that six extractions with chloroform take up nearly all of the esters.

Alkylation of Mercury Salt

A known weight of Hg salt which has been dried at 125 degrees and kept in a dessicator is weighed into a

glass tube with about one-half inch bore and six inches in length, which has been drawn out, and sealed at one end. The method of tares is used for weighing in the mercury salt. This eliminates the error of condensation of moisture upon the glass tubes, air displacement, etc. This same method if used later for the weights of the porcelain evaporating dishes used.

Knowing the weight of the Hg salt, one draws out the tube to a capillary constriction. To the cooled tube, is added enough alkyl iodide for complete esterification, and sufficient solvent to keep in solution all the ester formed.

Quantities Found to be Best for Experiments

0.5 gm. Hg salt
2 c.c. alkyl iodide
5 c.c. of solvent.

After the addition of these substances, the tubes are chilled by an ice mixture, and then sealed. After sealing, they are heated at different temperatures for different lengths of time.

Different solvents may be used and also different alkyl iodides. Hence, in this way, one can find the effects of temperature, period of heating, solvent, and alkyl iodides upon the ratio of the esters.

KCN Method of Extraction of Esters

After esterification, the tube is cooled and opened by scratching and the application of a hot glass rod.

The contents of the tube are brought into an extraction funnel by means of a funnel. The tube is carefully washed with about 2 c.c. $CHCl_3$ portions three times. The tip end of the tube is washed off with $CHCl_3$ after each washing. Open the other end. Wash out the tubes with 3 c.c. KCN until all of the insoluble HgI_2 is dissolved. Also dissolve out HgI_2 in tips by KCN. Now wash with water, and as a final washing use $CHCl_3$. These washings must be done quantitatively and with care. Washing can be done readily by revolving the tube in a horizontal position between the thumb and forefinger of each hand. After extraction, the mixture and washings are in the extraction funnel. To this is added about 50 c.c. H_2O and a few drops of an NaOH solution to alkalinity, by using phenolphthalein as an indicator.

As a precaution, there are added a few drops of an $Na_2S_2O_3$ solution, to dissolve any iodine which may have been set free from the alkyl iodide. Iodine being insoluble in $CHCl_3$ would be left with the esters upon evaporation of $CHCl_3$ extract and would cause an over-weight. Although iodine is volatile in the air, it would not go off from the esters, due to occlusion or adsorption.

Iodoform, which may be formed when alcohol is used as a solvent, was found to volatilize upon the standing of the esters.

As the esters were found to be slightly volatile with a rise in temperature, they can not be heated to drive off either the iodine or iodoform.

The volume of $CHCl_3$ in the extraction funnel is made 15 c.c. and the mixture is shaken until the $CHCl_3$ extract is colorless.

The $CHCl_3$ is then run into a second extraction funnel containing 50 c.c. of H_2O slightly alkaline, and then is carefully washed and run into an evaporating dish of known weight. It was found that all of the ester formed could be extracted by five more extractions of 5 c.c. portions of $CHCl_3$. They are treated similarly to the first.

After each shaking of the extraction funnel, the funnel should be inverted and pressure released by the opening of the pet-cock.

The stoppers and necks of funnels should be carefully washed with $CHCl_3$.

After the transference of the $CHCl_3$ extract from one funnel to the other or from the funnel to the dish, the last traces of the $CHCl_3$ extract shoubd be driven out by the gentle application of a capillary gas flame. The tips should always be washed with $CHCl_3$ after each operation.

Quantities of the solvent and alkyl iodide used should be evaporated in check experiments to see that no residue is obtained. Also all solutions used should be extracted with $CHCl_3$ until no residue is left, upon evaporation.

A check tube consisting of the solvent, alkyl iodide, should be run and extracted with $CHCl_3$ in the presence of $Na_2S_2O_3$ and 50 c.c. alkaline water for weighable residue. A check tube consisting of the solvent and Hg salt should be run similarly for weighable residue. These two tubes should be heated to the highest temperature to be used and for the longest period of time.

The $CHCl_3$ extract of about 50 c.c. is evaporated on a steam bath in a weighed evaporating dish. Gentle blowing on the surface during the evaporation prevents boiling and creeping at such high temperatures . All but a few c.c. of $CHCl_3$ is evaporated off in this way, and the rest goes off by blowing at room temperatures. The dish is then put into a vacuum dessicator and allowed to come to constant weight. Knowing the weight of the dish empty and the dish and ester, we can get the weight of the esters formed.

The porcelain dishes including the tar are always kept in the vacuum dessicator.

When the method was first tried, there were two alternatives:

First.--Bring the reaction mixture into the extraction funnel, etc., as above described.

Second.--Evaporate the solvent in a porcelain dish, thus eliminating the possibility of a loss in esters by the solubility of the solvent in the alkaline water solution. The residue was then taken up by $CHCl_3$ and brought into the extraction funnel. This also would eliminate the greater part of the HgI_2 formed.

Experiment

About 0.5 gm. of Hg salt + 2 c.c. CH_3I + 5 c.c. ether were heated at 100° for two to three hours and extracted by the first method. The weight of the esters was 0.109 grams. Another tube run along with this one and extracted by the second method gave as the weight of esters 0.0406 grams. This either shows a loss during evaporation or an adsorption of the esters by HgI_2 which was left in evaporating dish when the solvent was evaporated. Hence, the first method was adopted.

All solutions should be checked about every three weeks.

Hydrolysis of Esters

After the esters have come to constant weight, they are transferred by chloroform to a glass tube drawn out at one end. The tube is then chilled and drawn out to a constrictioh. The $CHCl_3$ is then "tickled" off, or

boiled, by means of a small glass rod over a steam bath, to prevent bumping.

Three c.c. of a solution of alcohol saturated with HCl gas is then added. The tube is sealed and heated from one to two hours at 100 degrees. This converts the oxygen ester into the free acid which is neutralized with alkali and is not extracted by the chloroform used to take up the N-ester.

Hence, by the method of extraction used above, we can obtain the pure N-ester and by evaporating off the $CHCl_3$ in a weighed porcelain dish, the weight of the ester is obtained.

Care should be taken when the hydrolysis tubes are opened, as the pressure upon the inside is sometimes troublesome; and also when transferring contents to the extraction funnel, as "spitting" often takes place, due to occluded gases. Five cubic centimeters of the hydrochloric acid gas in the alcoholic saturated solution should be evaporated down for a weighable residue.

Another method was tried in which it was attempted to drive off $CHCl_3$ after transference of the esters to the hydrolysis tube:

The heat was supplied by a round electrical stove, over which was put an ether can. The whole was surrounded by an asbestos board. The tubes were held erect by insertion through an asbestos board with holes

cut in it and then tips were allowed to rest on the ether can. Evaporation in this way requires a tube with no constriction. This idea worked nicely but the time required was so long as to make it valueless. It has been found that the best method for evaporating the chloroform off from the porcelain dishes is by heating over a steam bath and gentle blowing upon the surface to prevent ebullition and creeping. Other means such as fans, air lines, etc., were tried as a substitute for blowing, but were found to always deposit dust and dirt, whereas by blowing, the lungs act as a filter for such dust and dirt particles which float in the air.

MERCURY SALT OF THE SULFONE, AND METHYL IODIDE IN ALCOHOL, ETHER, OR BENZENE AT 50° AND 100°

Table 1

No.	Sulfone (Gms.)	Alkyl Halide	Solvent	Heated	Temp.	Esters (Gms.)	Hydrolysis Heat 100°	N-ester (Gms.)	% N-ester
I	0.3460	2 cc. CH_3I	5 cc. abs.alc	4 hours	100°	0.04285	3 cc. HCl alc	0.0372	86.81
II	0.4411	Do.	Do.	Do.	100°	0.04705	Do.	0.0413	87.76
III	0.3050	Do.	Do.	8 hours	50°	0.04925	Do.	0.0409	83.10
IV	0.5328	2 cc. CH_3I	5 cc. ether	8 hours	50°	0.1655	3 cc. HCl alc	0.1576	95.20
V	0.5220	Do.	Do.	4 hours	100°	0.0897	Do.	0.0830	92.50
VI	0.4725	Do.	Do.	Do.	100°	0.1019	Do.	0.0968	90.50
VII	0.5502	Do.	Do.	8 hours	100°	0.2577	Do.	0.2458	95.40
VIII	0.5042	2 cc. CH_3I	5 cc. benzene	8 hours	50°	0.3401	3 cc. HCl alc	0.2596	76.30
IX	0.4719	Do.	Do.	Do.	50°	0.3580	Do.	0.2701	75.65
X	0.4526	Do.	Do.	Do.	100°	0.3078	Do.	0.2212	71.80
XI	0.4397	Do.	Do.	8 hours	100°	0.3103	Do.	0.2159	69.50
XII	0.2828	Do.	Do.	4 hours	100°	0.2027	Do.	0.1497	73.80

PURE OXYGEN AND NITROGEN ESTERS IN BENZENE AND ALKYL HALIDE AT 100°

Table II

Sulfone	Ester	Weight	Alkyl Halide	Solvent	Heated	Weight	Hydrolysis	Weight N-ester	Per cent N-ester
Methyl	Ethyl oxygen	0.2571	2 cc. C_2H_5I	5 cc. benzene	3 hours	0.2579	Heat 1 hr.	0.0048	1.8
Do.	Ethyl nitrogen	0.1442	Do.	None	1.5 hrs.	0.1556	Do.	0.1468	101.8
Do.	Methyl nitrogen	0.1084	2 cc. CH_3I	5 cc. benzene	Do.	0.1107	Do.	0.1126	103.8
Do.	Methyl nitrogen	0.1187	Do.	None	Do.	0.1218	Do.	0.1211	102.0
Do.	Ethyl oxygen	0.2984	2 cc. C_2H_5I	None	8 hours	0.2995	Do.	0.0081	2.6
Do.	Ethyl oxygen	0.2162	Do.	5 cc. benzene	Do.	0.2179	Do.	0.0052	2.3

The ratios in Table I vary somewhat. Experiments V, VI, X, and XI, however, were completed during the working out of the KCN method and are subject to larger errors. The other experiments check these very closely, however, although not quite as satisfactorily as desired.

In Table II, the oxygen ester used was prepared from the Hg salt, which gives about 97 per cent oxygen ester. This was recrystallized once from alcohol, which would not eliminate all the N-ester present, as is seen from the above table.

The experiments with the nitrogen ester show an increase in ester, but this increase is within experimental errors. In fact, it appears as if this 2-3 per cent might be an impurity, as it shows a constant value throughout.

Conclusions

The mercury salt of 1-phenyl-4,5-dihydro-5-oxy-3-triazolyl methyl sulfone gives with methyl iodide in a given solvent a constant ratio of enol and keto esters independent of concentration, time of heating, and temperature. In ether, in absolute ethyl alcohol, and in benzene, the proportion of keto ester formed is about 93 per cent, 85 per cent, and 75 per cent, respectively, of the total ester. Such esters must be formed by independent side reactions as they do not rearrange into each other in the presence of alkyl halides, or alkyl halides and benzene, as solvent.

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